Administration of compositions of the present invention may be carried out in combination with the administration of other agents. For example, it may be desired to administer an opioid antagonist, such as naloxone, if a compound exhibits opioid activity where such activity may not be desired. The naloxone may antagonize opioid activity of the administered compound without adverse interference with the antiarrhythmic activity. As another example, an aminocyclohexyl ether compound of the invention may be co-administered with epinephrine in order to include local anesthesia.

In order to assess whether a compound has a desired pharmacological activity with the present invention, it is subjected to a series of tests. The precise test to employ will depend on the physiological response of interest. The published literature contains numerous protocols for testing the efficacy of a potential therapeutic agent, and these protocols may be employed with the present compounds and compositions.

For example, in connection with treatment or prevention of arrhythmia, a series of four tests may be conducted. In the first of these tests, a compound of the present invention is given as increasing (doubling with each dose) intravenous boluses every 8 minutes to a pentobarbital anesthetized rat. The effects of the compound on blood pressure, heart rate and the ECG are measured 30 seconds, 1, 2, 4 and 8 minutes after each dose. Increasing doses are given until the animal dies. The cause of death is identified as being of either respiratory or cardiac origin. This test gives an indication as to whether the compound is modulating the activity of sodium channels and/or potassium channels, and in addition gives information about acute toxicity. The indices of sodium channel blockade are increasing P-R interval and QRS widening of the ECG. Potassium channel blockade results in Q-T interval prolongation of the ECG.

A second test involves administration of a compound as an infusion to pentobarbital anesthetized rats in which the left ventricle is subjected to electrical square wave stimulation performed according to a preset protocol described in further detail below. This protocol includes the determination of thresholds for induction of extrasystoles and ventricular fibrillation. In addition, effects on electrical refractoriness are assessed by a single extra beat technique. In addition effects on blood pressure,

in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 9.0 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 20 mL) (1.30 g, 51.6 mmol), in dry dimethylformamide (50 mL) was added via cannula a solution of 1-naphthenethanol (6.8 g, 40 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of gas and the reaction mixture was stirred at room temperature for 4 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the slurry of alcoholate. The reaction mixture was heated to 80°C for 3 hours, then the temperature was reduced to 35°C for overnight stirring. The reaction mixture was poured into ice-water (1500 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (500 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 12.0 g of an oil which was dissolved in ether (80 mL) and treated with a saturated solution of HCl in ether. A sticky product came out of solution, the solvent was evaporated *in vacuo* and the resulting crude hydrochloride salt was dissolved in water (200 mL). The acidic aqueous solution was extracted with ethyl ether (2 x 100 mL) and then basified to pH 10 with 50% sodium hydroxide aqueous solution. The basic aqueous solution was extracted with ethyl ether (2 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 7.20 g of the crude free amino ether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent to provide the pure free base. The product was dissolved in ethyl ether (80 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ethyl ether (80 mL). A white product precipitated and this solid was collected and dissolved in the minimum amount of warm ethyl alcohol; addition of a large volume of ethyl ether triggered

dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 7.4 g of an oil which was dissolved in ether (80 mL) was treated with a saturated solution of HCl in ether. An oil came out of solution, the solvent was evaporated *in vacuo* and the residue was dissolved in water (100 mL). The acidic aqueous solution was extracted with ethyl ether (2 x 50 mL) and then basified to pH 10 with 50% sodium hydroxide aqueous solution. The basic aqueous solution was extracted with ethyl ether (2 x 50 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 3.67 g of the crude free amino ether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent to provide the pure free base. The product was dissolved in ethyl ether (30 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ethyl ether (30 mL). The solvent was evaporated and the residue dissolved in the minimum amount of ethyl alcohol, addition of a large volume of ethyl ether triggered crystallization. The crystals were collected to afford 1.31 g of the title compound, m.p. 148-151°C, having the elemental analysis indicated in Table 1.

EXAMPLE 4

(±)-TRANS-[2-(4-MORPHOLINYL)-1-[2-(2-NAPHTHOXY)ETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #4)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50

EXAMPLE 5

(±)-TRANS-[2-(4-MORPHOLINYL)-1-[2-(4-BROMOPHENOXY)ETHOXY)]]CYCLOHEXANE MONOHYDROCHLORIDE

(COMPOUND #5)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 3.95 g (92% yield) of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.63 g, 26 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 2-(4-bromophenoxy)ethanol (4.34 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The reaction mixture was heated to 90°C for 90 min. and then the temperature was reduced to 40°C and the reaction was stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution (300 mL) of sodium chloride and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 8.35 g of a yellow oil which was dissolved in ether (100 mL) and treated with a saturated solution of HCl in ether (100 mL). The resulting white solid was collected and recrystallized in

boiling ethanol (150 mL) to yield 3.7 g (54% yield) of the pure title compound, m.p. 228-230°C, having the elemental analysis indicated in Table 1.

EXAMPLE 6

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(3,4-DIMETHOXYPHENETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE

(COMPOUND #6)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.18 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.64 g, 27 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 3,4-dimethoxyphenethyl alcohol (3.64 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The reaction mixture was heated to 80°C for 90 min. and then the temperature was reduced to 40°C and stirring continued overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 7.18 g of the

HCl aqueous solution (580 mL) and water (400 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to leave 54.5 g of amber oil, which was further pumped under high vacuum with stirring at room temperature for 25 min. to give 52.08 g (5.6% over theoretical yield) of the crude title compound suitable for the next step without any further purification.

(iii) 7-Benzyloxycarbonyl-1,4-dioxa-7-azaspiro[4.4]nonane:

A mixture of N-benzyloxycarbonyl-3-pyrrolidinone (51.98 g, step ii, no more than 224.9 mmol) and ethylene glycol (18.8 mL, 99+%, 337.4 mmol) in toluene (180 mL) with a catalytic amount of *p*-toluenesulfonic acid monohydrate (1.04 g, 5.4 mmol) was refluxed in a Dean & Stark apparatus for 16 hours. The reaction mixture was then diluted with more toluene (250 mL) and washed with saturated sodium bicarbonate aqueous solution (150 mL) and saturated sodium chloride aqueous solution (2 x 150 mL). The combined aqueous layers were back-extracted with toluene (100 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 79.6 g of dark oil. The crude product was dissolved in ethanol (500 mL), and running it through a bed of activated carbon (80 g), decolorized the resulting solution. The charcoal was washed with more ethanol (1000 mL) and toluene (500 mL). The filtrate was concentrated *in vacuo* and further pumped under high vacuum for 1 hour to yield 63.25 g (6.8% over theoretical yield) of the crude title compound suitable for the next step without any further purification.

(iv) 1,4-Dioxa-7-azaspiro[4.4]nonane: A mixture of 7-benzyloxycarbonyl-1,4-dioxa-7-azaspiro[4.4]nonane (34.79 g, step iii, no more than 123.7 mmol) and 10% Pd-C (13.9 g) in ethanol (90 mL) was hydrogenolyzed (60 psi) in a Parr shaker apparatus at room temperature for 1.5 hour. The catalyst was filtered off, the solvent was evaporated *in vacuo* and the residue was pumped under high vacuum for 20 min. to yield 15.86 g of the title compound (yield 99.3%).

(v) (1R,2R)/(1S,2S)-2-(1,4-Dioxa-7-azaspiro[4.4]non-7-yl)cyclohexanol: A mixture of 1,4-dioxa-7-azaspiro[4.4]nonane (23.54 g, step iv, no more than 182 mmol), cyclohexene oxide (22.6 mL, 98%, 219 mmol) and water (7.8 mL) was heated at 80°C for 2 hours. The reaction mixture was then partitioned between

adjusted to pH 5.5. Extraction with diethyl ether (3 x 50 mL) followed by drying over sodium sulfate and concentration *in vacuo* provided the pure aminoether. The hydrochloride salt was precipitated by treatment of the free base with ethereal HCl. Recrystallization from a mixture of acetone-methanol-diethyl ether yielded 2.6 g (68% yield) of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 23

(1R,2R)/(1S,2S)-2-(3-KETOPYRROLIDINYL)-1-[(2,6-DICHLOROPHENYL)METHOXY]CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #23)

Compound #23 was prepared in 7 steps according to the procedure detailed in Example 15. Steps (i) to (v) were identical to the ones described in Example 15. The ether synthesis (step vi) was carried out according to the Williamson ether synthesis as in Example #22.

(vi) (1R,2R)/(1S,2S)-2-[1,4-Dioxa-7-azaspiro[4.4]non-7-yl]-1-[(2,6-dichlorophenyl)methoxy] cyclohexane: To a suspension of sodium hydride, 80% oil dispersion (222 mg, 7.25 mmol) in ethyleneglycol dimethyl ether (20 mL) was added a solution of (1R,2R)/(1S,2S)-2-(1,4-dioxa-7-azaspiro[4.4]non-7-yl)cyclohexanol (1.5 g, 6.60 mmol, step (v) of Example 15) in ethylene glycol dimethyl ether (10 mL). The resulting mixture was stirred at room temperature for 2 hours and then a solution of 2,6-dichlorobenzyl bromide (1.9 g, 7.9 mmol) in ethylene glycol dimethyl ether (10 mL) was added. The reaction mixture was refluxed for 16 hours under argon atmosphere, the solvent was evaporated *in vacuo* and the residue was taken up with water (70 mL). The aqueous solution was acidified to pH 0.5 with 6M HCl aqueous solution and then extracted with diethyl ether (2 x 40 mL). Basification of the aqueous solution to pH 4.5-5.5, followed by extraction with diethyl ether (4 x 40 mL), drying of the combined organic extracts over sodium sulfate and evaporation of the solvent *in vacuo* provided the intermediate title compound.

Table 3

Compound	$ED_{50}AA$
#1	0.8
#2	1.0
#3	2.1
#4	2.0
#5	3.0
#6	4.0
#7	4.0
#8	1.0
#9	1.0
#10	2.0
#11	1.0
#14	1.5
#15	0.43
#17	1.1
#19	1.4
#21	1.4
#22	1.8
#23	2.1
#24	0.6
#25	2.5
#26	6.5

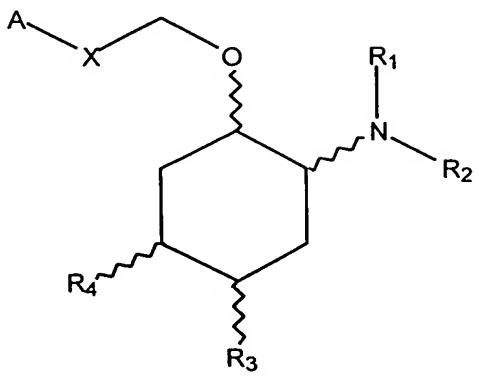
EXAMPLE 29

MEASUREMENT OF ECG PARAMETERS

Rats weighing 200-250 gms were used in this example. Animals were anesthetized with 60 mg/kg pentobarbitone i.p. The carotid artery and jugular vein were cannulated for measurement of blood pressure and drug injection, respectively. ECG was recorded by insertion of electrodes placed along the anatomical axis of the heart. All compounds were given as bolus injections.

Various ECG parameters were measured. Table 4 describes the results of the tests as ED_{25} (micromol/kg) which are the doses required to produce a 25% increase in the parameter measured (ne = not estimated). The increases in P-R interval and QRS interval indicate cardiac sodium channel blockage while the increase in Q-T interval

54. A compound of claim 49 having formula (XIII), or a solvate or pharmaceutically acceptable salt thereof:



(XIII)

wherein, independently at each occurrence,

X is selected from a direct bond and -CH=CH-;

R_1 and R_2 are defined as in claim 49;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_3-C_8cycloalkyl and any of formulae (III), (IV), (V), (VI), (VII) and (VIII) as defined in claim 49, where R_8 and R_9 are defined as in claim 49, R_7, R_{10}, R_{11} and R_{12} are hydrogen, and Z is selected from O, S and N-R_{17} where R_{17} is selected from hydrogen and methyl; with the proviso that A may be selected from formulae (VII) and (VIII) only when X is a direct bond;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.